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Prevention of orofacial clefts caused by smoking: implications of the Surgeon General's Report

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Abstract

Introduction—According to the 2014 Surgeon General's Report, smoking in early pregnancy can cause orofacial clefts. We sought to examine the implications of this causal link for the potential prevention of orofacial clefts in the United States.

Methods—Using published data on the strength of the association between orofacial clefts and smoking in early pregnancy and the prevalence of smoking at the start of pregnancy, we estimated the attributable fraction for smoking as a cause of orofacial clefts. We then used the prevalence of orofacial clefts in the United States to estimate the number of orofacial clefts that could be prevented in the United States each year by eliminating exposure to smoking during early pregnancy. We also estimated the financial impact of preventing orofacial clefts caused by maternal smoking based on a published estimate of attributable healthcare costs through age 10 for orofacial clefts.

Results—The estimated attributable fraction of orofacial clefts caused by smoking in early pregnancy was 6.1% (95% uncertainty interval 4.4%, 7.7%). Complete elimination of smoking in early pregnancy could prevent orofacial clefts in approximately 430 infants per year in the United States, and could save an estimated $40.4 million in discounted healthcare costs through age 10 for each birth cohort.

Conclusion—Understanding the magnitude of the preventable burden of orofacial clefts related to maternal smoking could help focus smoking cessation efforts on women who might become pregnant.

Keywords

Smoking; orofacial clefts; prevention; healthcare costs

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The 50th anniversary Surgeon General's Report released in January 2014 marked the first confirmation of the causal link between smoking in early pregnancy and orofacial clefts.[1] The association is consistent across a variety of study designs, populations, and settings. The association is also robust to corrections for likely levels of exposure misclassification anticipated in self-reported smoking data.[2] In addition, smoking in pregnancy was associated with an increased risk of orofacial clefts in a study that used objective measures of smoking based on midpregnancy serum cotinine levels.[3] The consistency of the findings across a large number of studies in combination with biological plausibility supported the conclusion of causality in the 2014 report.[1] Although the magnitude of the association between smoking and clefts is relatively modest, this represents one of the few known risk factors for orofacial clefts with potential for prevention. And, quantifying the annual preventable number of orofacial clefts could help reinforce the value of smoking prevention efforts targeting women at risk of pregnancy.

Methods

We estimated the annual number of orofacial clefts that could be prevented in the United States with elimination of smoking in early pregnancy, using the same methodology employed in a previous analysis modeling the impact of prepregnancy obesity on adverse fetal and infant outcomes.[4] The strength of the association between orofacial clefts and smoking was based on the most recent meta-analysis of this association.[5] Data from the Pregnancy Risk Assessment Monitoring System in 27 states on women reporting smoking just before pregnancy was used as an estimate of smoking prevalence in the first few weeks of pregnancy, before many pregnancies are recognized, because orofacial clefts occur early in pregnancy.[6]

We used standard methods for the calculation of the attributable fraction (AF), where the AF is a function of the prevalence of smoking just before pregnancy (P[D]) and the OR estimating the strength of the association.[7] The AF was then multiplied by the estimated annual number of orofacial clefts in the United States to estimate the preventable number associated with smoking in early pregnancy.

$$AF = \frac{P[D] * (OR - 1)}{1 + P[D] * (OR - 1)} \quad \text{[Equation 1]}$$

Equation 1 is an unbiased estimate of the AF when using the crude OR (not adjusted for confounders). The AF estimates could be biased if there is confounding of the association between exposure (smoking in early pregnancy) and the outcome (orofacial clefts).[7] While the published meta-analysis we used was based on some adjusted ORs and some unadjusted ORs, the authors found little evidence of confounding. There were very similar results for the association between smoking and orofacial clefts whether based on all studies (summary OR = 1.28) or the based only on those studies with adjusted estimates (summary OR = 1.26).[5]

The annual number of orofacial clefts occurring in the United States was based on the most recent national prevalence estimates combining data from multiple population-based state

surveillance systems, and the estimates for cleft lip with or without cleft palate and cleft palate alone were combined into one estimate for orofacial clefts (Table 1).[8] The attributable fraction was multiplied by the annual number of clefts to estimate the preventable number and associated uncertainty interval.

We used the difference in average healthcare costs for children with isolated orofacial clefts (no other major birth defects and no syndromes) and children without orofacial clefts from ages 0 to 10 to estimate the attributable healthcare costs (per child) that could be avoided with the prevention of smoking-related orofacial clefts for each birth cohort. The cost data come from 2004 nationwide claims data for children with private health insurance.[9] Costs were adjusted for inflation to 2013 US dollars using the Personal Consumption Expenditures price index for health care.[10] The present value of healthcare costs was calculated using a 3% per annum discount rate for costs at ages after infancy.

Results

Based on the published inputs on the strength of the association between smoking and orofacial clefts (OR = 1.28, 95% confidence interval 1.20—1.36) and the prevalence of smoking at the start of pregnancy (23.2%, 95% confidence interval 22.4—23.9; Table 1), the estimated attributable fraction of orofacial clefts due to smoking in early pregnancy was 6.1% (95% uncertainty interval 4.4%, 7.7%). Given the estimated numbers of children born with orofacial clefts in the United States, the complete elimination of smoking in early pregnancy could prevent an estimated 430 infants per year (95% uncertainty interval 310, 550) from being born with an orofacial cleft. The present value of healthcare costs that could be saved with the prevention of all orofacial clefts caused by smoking is estimated at $40.4 million (uncertainty interval $29.3 million – $51.3 million) for each annual cohort of 430 averted cases (Table 2).

Discussion

Eliminating smoking exposure before pregnancy or in the first few weeks of pregnancy could prevent between 310 and 550 cases of orofacial clefts each year in the United States. While the causes of most orofacial clefts are unknown, the confirmation that smoking exposure in early pregnancy can cause orofacial clefts highlights an important prevention opportunity to improve the health of infants. This finding emphasizes the importance of expanding smoking cessation efforts targeting reproductive aged women.

Smoking during pregnancy increases the risk for fetal growth restriction, preterm delivery, stillbirth, and perinatal mortality.[1] While complete elimination of exposure to smoking during pregnancy is optimal for reducing risks, smoking cessation during pregnancy can significantly attenuate the risks of some adverse reproductive outcomes, such as low birth weight and stillbirth.[1] In contrast, orofacial clefts occur very early in pregnancy, and smoking cessation subsequent to recognition of pregnancy is unlikely to reduce the exposure during the critical time period. Thus, for effective prevention of orofacial clefts smoking cessation efforts need to be targeted more broadly to reproductive aged women and need to occur prior to pregnancy.

While the specific biological mechanism through which smoking causes some orofacial clefts is not known, there are several plausible pathways. Smoking in early pregnancy might affect fetal development by causing fetal hypoxia or by impacting maternal nutritional status such as the reductions in serum folate levels that occur with smoking.[1] There could also be teratogenic effects of one or more components of tobacco smoke including nicotine, carbon monoxide, heavy metals such cadmium, or polycyclic aromatic hydrocarbons; or, the teratogenicity of smoking could be mediated through the combination of these exposures.[1] However, a clear understanding of the specific mechanism is not a prerequisite for successful prevention efforts.

The high prevalence of unintended pregnancy in the United States and the comparatively higher prevalence of smoking among those with unintended pregnancy underscore the need for smoking cessation efforts directed towards all reproductive aged women and not just those planning to become pregnant. In addition, the prevalence of prepregnancy smoking is much higher among those women delivering a liveborn infant who reported that their pregnancy was unintended. Among 26 states participating in the Pregnancy Risk Assessment Monitoring System in 2004, the prevalence of prepregnancy smoking among women who had an intended pregnancy was 17.6%, compared with 30.9% among women with unintended pregnancies.[11]

Estimation of the attributable fraction and preventable number for orofacial clefts demonstrates an important and quantifiable health impact of eliminating smoking throughout pregnancy, including during early pregnancy when most birth defects occur. And, given the high healthcare costs associated with the care of those with isolated orofacial clefts and even higher costs for those with multiple major defects or other co-morbidities, the return on investment of prevention activities targeted to the preconception period is expected to be favorable.

The prevalence of smoking in a community appears to be a more powerful predictor of smoking during pregnancy even with targeted counseling intervention suggesting a potential role for community-wide interventions.[12] Public health authorities recommend that states and communities adopt and implement programs and policies to influence societal organizations, systems, and networks that encourage and support individuals to make behavior choices consistent with tobacco-free norms.[13] It has been demonstrated that smoke-free laws reduce the prevalence of smoking among low-income women prior to pregnancy and reduce the incidence of preterm births;[14,15] such legislation might reduce the incidence of orofacial clefts as well.

The Surgeon General’s conclusion that smoking in early pregnancy can cause orofacial clefts should serve as a call to action to eliminate smoking prior to pregnancy and should thereby positively impact the health of hundreds of infants each year. Reduction of prepregnancy smoking prevalence in the United States will promote the health of both women and infants, and provide health benefits that extend far beyond the prevention of orofacial clefts.

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Table 1

Model inputs for estimating the impact of preventing orofacial clefts caused by smoking in early pregnancy.

Model inputs	Point estimate and uncertainty
Prevalence of smoking just before pregnancy in 2010[6]	23.2% (95% confidence interval 22.4 – 23.9)*
Association between smoking in early pregnancy and orofacial clefts[5]	Odds ratio = 1.28 (95% confidence interval 1.20 – 1.36)
Annual number of births with orofacial clefts in the U.S during 2004–2006. [8]	
Cleft lip with or without cleft palate	4,437 (95% confidence interval 4,304 – 4,570)
Cleft palate alone	2,651 (95% confidence interval 2,549 – 2,754)
Total orofacial clefts	7,088 (95% confidence interval 6,919 – 7,256)†
Mean healthcare costs for a child from age 0–10 with an isolated orofacial cleft (no other major birth defects and no syndrome) [9]	$93,599††

*Self-reported smoking just before pregnancy is used as a proxy for the exposure to smoking in the first few weeks of pregnancy

†Monte Carlo sampling method was used to estimate 95% CI for combined orofacial clefts based on the confidence intervals available for cleft palate alone and cleft lip with or without cleft palate.

††This estimate is in 2013 dollars using an inflation adjustment of 1.25 from 2004 prices to 2013 prices from the Personal Consumption Expenditures price index for healthcare costs from the Bureau of Economic Analysis and is a present value calculated using an annual discount rate of 3% for costs beyond infancy.

Table 2

Estimates of the attributable fraction and preventable number for orofacial clefts caused by smoking in early pregnancy, and the estimated resulting childhood healthcare costs in the United States per year.

Parameter Estimated	Estimates (mean of the simulations) and Uncertainty Intervals
Attributable fraction for orofacial clefts caused by smoking in early pregnancy	6.1% (4.4% – 7.7%)
Annual preventable number of orofacial clefts*	430 (310 – 550)
Estimate of potential cost savings (through age 10) with prevention of orofacial clefts caused by smoking †	$40.4 million ($29.3 million – $51.3 million)

*Preventable number is rounded to the nearest 10.

†Cost estimate is rounded to the nearest $100,000.